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International application number: PCT/US04/043997

International filing date: 23 December 2004 (23.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/531,955
Filing date: 23 December 2003 (23.12.2003)

Date of receipt at the International Bureau: 09 February 2005 (09.02.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

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**APPLICATION NUMBER:** *60/531,955*
**FILING DATE:** *December 23, 2003*
**RELATED PCT APPLICATION NUMBER:** *PCT/US04/43997*

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PTO/SB/16 (2-01)
Approved for use through 10/31/2002. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Docket Number: 225630

# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

**This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).**



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**TITLE OF THE INVENTION (280 characters max)**

SUBSTITUTED MELATONIN DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND METHODS OF USE

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**ENCLOSED APPLICATION PARTS (check all that apply)**

☒ Specification *Number of Pages:* 22
*(including any claims and abstract)*
☐ Drawings *Number of Sheets:*
☒ Application Data Sheet. See 37 CFR 1.76
☐ Power of Attorney
☐ Assignment
☐ CD(s), Number
☐ Other (specify)

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☒ Applicant claims small entity status. See 37 CFR 1.27.
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FILING FEE AMOUNT: $80.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Governm nt:
☐ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

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CERTIFICATION UNDER 37 CFR 1.10

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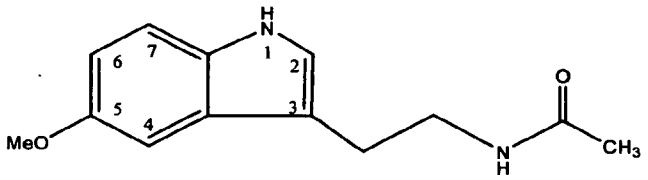
# SUBSTITUTED MELATONIN DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND METHODS OF USE

## FIELD OF THE INVENTION

**[0001]** The present invention relates to derivatives of melatonin. More particularly, the invention provides aryl substituted melatonin derivatives, methods of preparation thereof, pharmaceutical compositions comprising aryl substituted melatonin derivatives, and methods of using same.

## BACKGROUND OF THE INVENTION

**[0002]** Melatonin (N-acetyl-5-methoxytryptamine), formula (I),




(I)

is a neurohormone produced primarily by the pineal gland, and to a lesser extent by extra pineal tissues such as the retina, harderian gland, and gastrointestinal tract. The synthesis of melatonin is regulated by circadian and seasonal variations in day length through a polysynaptic neuronal pathway from the retina to the pineal gland. Studies indicate that melatonin is involved in the transduction of photoperiodic information and appears to modulate a variety of neural and endocrine functions in vertebrates, including the regulation of reproduction, body weight, and metabolism in photoperiodic mammals, as well as the control of circadian rhythms and the modulation of retinal physiology. Melatonin has been detected in numerous central and peripheral tissues using the specific radioligand 2-[$^{125}$I]-iodomelatonin described in Delagrange et al., *Clin. Neuropharmacol.*, *20*, 482 (1997). Many of the effects of melatonin are mediated through high affinity G-protein-coupled receptors expressed primarily in the brain, retina, pituitary, and blood vessels (see, e.g., Mahle et al., *J. Biol. Rhymthms*, *12*, 690 (1997)).

**[0003]** The search for novel high-affinity melatonin ligands has led to the synthesis of numerous indole and non-indole melatonin derivatives, and the elucidation of a structure - activity relationship for melatonin binding affinity (see, e.g., Methe-Allainmat et al., *Expert Opin. Ther. Pat.*, *7*, 1447 (1997), and Mor et al., *Curr. Med. Chem.*, *6*, 1875 (1998)). The melatonin derivatives were reported to be useful for treating desynchronization disorders (see, e.g., U.S. Patent 6,180,657), and mammalian breast carcinoma in combination with antiestrogen compounds (see, e.g., U.S. Patent 5,196,435). Melatonin derivatives also have

been used as an antioxidant (see, e.g., U.S. Patent 6,436,984), as well as a general anesthetic (see, e.g., U.S. Patent 6,552,064). A general anesthetic is one which causes a patient to lose consciousness. This type of agent often is referred to as a "hypnotic" agent.

**[0004]** Low-level dosing of oral melatonin in a sublingual fashion has been shown to be effective for pre-medication prior to administering a general anesthetic (see, e.g., *British Journal of Anesthesia, 82(6)*, 875-80 (1999)). In addition, U.S. Patent 6,552,064 discloses the use of melatonin as a general anesthetic. Experiments disclosed therein demonstrate the effectiveness of melatonin for induction of general anesthesia in rats in comparison to other known anesthetics. Cumulative intravenous (IV) injection of divided doses of melatonin caused a progressive loss of righting reflex, grip strength, and eyelash reflex. The $ED_{95}$ (95% CI, for loss of righting reflex) of melatonin is 312 mg/ml, as compared to 8 mg/kg for thiopental, and 14.9 mg/kg for propofol. Bolus injection of 312 mg/ml of melatonin, or 10 mg/kg of propofol, caused an immediate loss of righting reflex.

**[0005]** There remains a need for new melatonin derivatives, and methods for using such derivatives to induce general anesthesia, hypnosis, or sleep in a subject. The invention provides such derivatives and methods. The inventive derivatives are more effective as an anesthetic than melatonin alone. Thus, the derivatives of the invention can be used in larger doses for general anesthesia, and in smaller doses for hypnosis, sedation, and sleep induction. These and other advantages of the invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

## BRIEF SUMMARY OF THE INVENTION

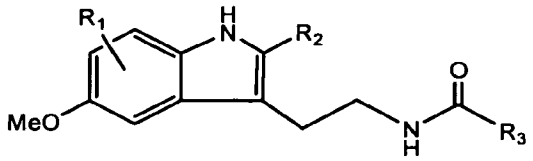
**[0006]** In one aspect of the invention, there are provided melatonin derivatives, such as 2-aryl substituted melatonin. In another aspect of the invention, there is provided a method of preparing the above-described 2-aryl substituted derivatives of melatonin. In various embodiments, the invention provides a pharmaceutical composition comprising a melatonin derivative as described above and a pharmaceutically acceptable carrier. In another aspect of the invention, there is provided a method of using melatonin derivatives to induce general anesthesia, sedation, hypnosis, and/or sleep effects in a patient. The invention also provides a method of using melatonin derivatives to treat a condition affected by melatonin activity in a patient, such as depression, epilepsy, jet-lag, work-shift syndrome, sleep and chronobiological disorders, glaucoma, reproduction, cancer, premenstrual syndrome, immune disorders, inflammatory articular diseases, neurodegenerative diseases of the central nervous system (e.g., Parkinson's disease or Alzheimer's disease), neuroendocrine disorders, cholestatic oxidative stress, neuroprotection (e.g., against A beta glutamate toxicity), sepsis and/or shock (e.g., induced by zymosan), myocardial dexorubicin toxicity, and for the

treatment of carbon tetrachloride-induced acute liver injury. The melatonin derivatives of the present invention can also be used as an analgesic and as a combination analgesic and anesthetic.

**[0007]** The melatonin derivatives of the present invention can also be used as a broad spectrum antioxidant as a free radical scavenger, to reduce lipid peroxidation, for the treatment of spinal cord ischemia, as a prophylactic for reperfusion damage, such as ischemic reperfusion, to ameliorate oxidative organ damage, and in reducing lead-induced neurotoxicity. The melatonin derivatives described herein are also useful as a protectant against side effects induced by other active pharmaceutical agents, such as against gastric damage induced by alend_____ sodium or omeprazole, against acetaminophen-induced side effects, against adriamycin-induced acute cardiac injury, in protecting against methotrixate hepatorenal oxidative innury, to treat chronic cyclosporin A nephrotoxity, as a protectant against cyclophosphamide-induced myelosuppression, as a protectant against cisplatin-induced renal injury, as a protectant for lung toxicity induced by chlorpyrifos-ethyl, oxidative stress caused by delta-amino-evulinic acid, bleomycin-induced pulmonary fibrosis to attenuate acute renal failure and oxidative stress induced by mercuric chloride, as a protectant against cellular damage caused by ionizing radiation, as a protectant against gentamicin-induced nephrotoxicity.

## DETAILED DESCRIPTION OF THE INVENTION

**[0008]** The aryl-substituted melatonin compounds in accordance with the present invention are represented by Formula II,




(II)

wherein,

$R_1$ is hydrogen, halo, or nitrate,

$R_2$ is $C_4$-$C_{20}$ aryl, and

$R_3$ is $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkoxy.

**[0009]** The following definitions are provided to better define the present invention. As used herein "halo" refers to fluoro, chloro, bromo, or iodo.

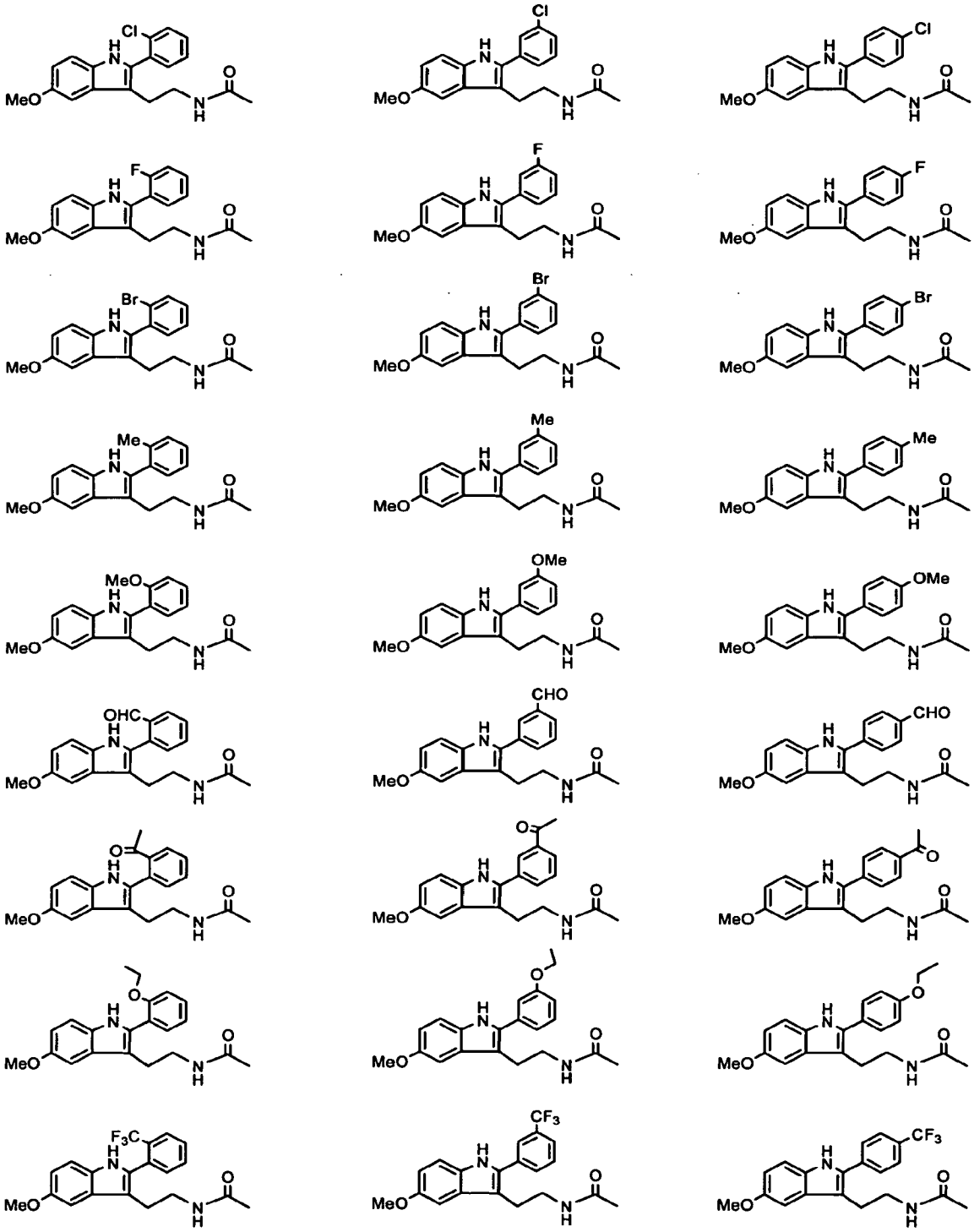
**[0010]** "$C_1$-$C_6$ alkyl" refers to straight or branched, substituted or unsubstituted, aliphatic groups of 1-6 carbon atoms including, for example, methyl, ethyl, propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, cyclobutyl, tert-butyl, pentyl, hexyl, and cyclohexyl.

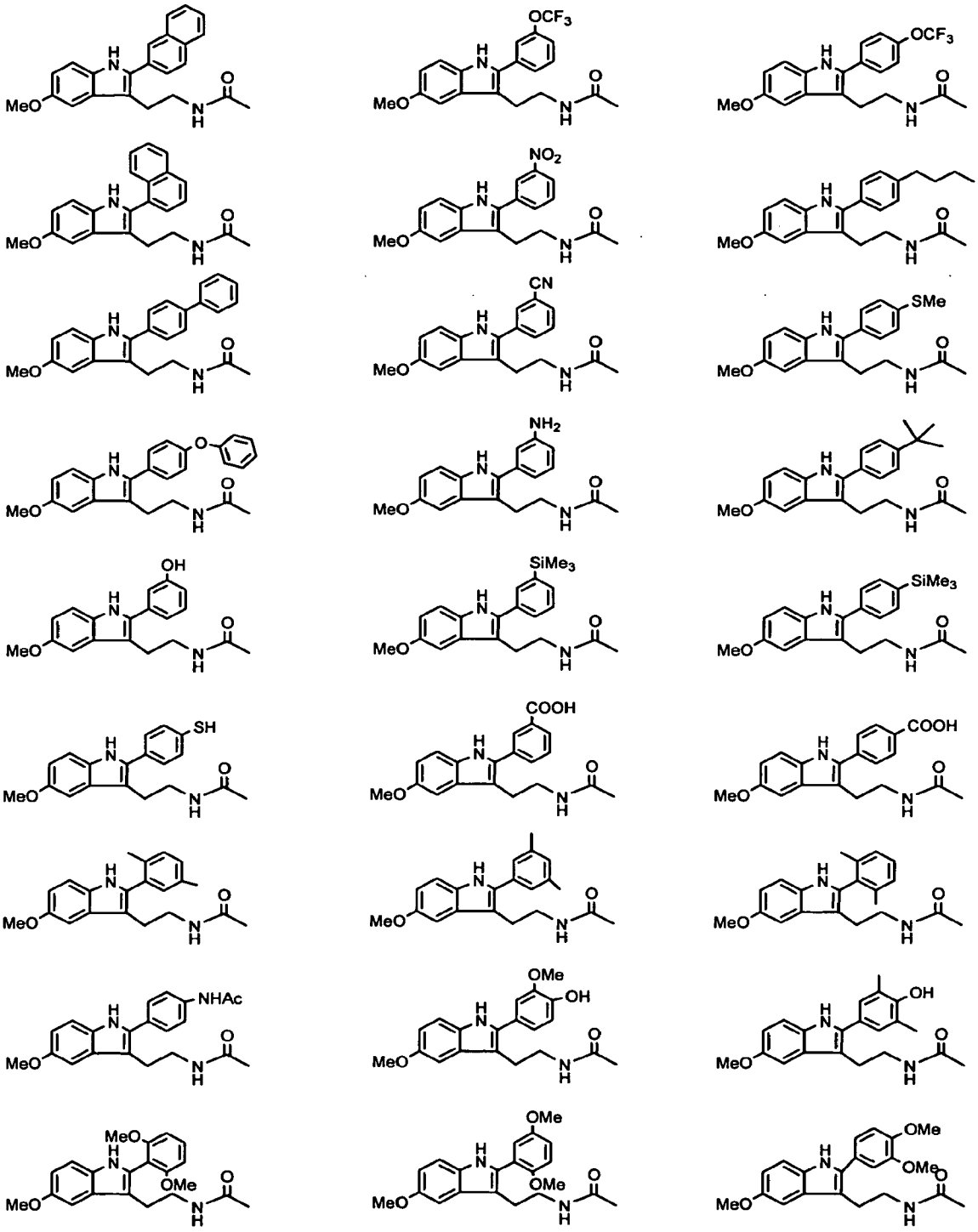
**[0011]** "$C_1$-$C_6$ alkoxy" includes straight or branched, substituted or unsubstituted, aliphatic ether functionalities of 1-6 carbon atoms such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, cyclohexoxy and phenoxy.

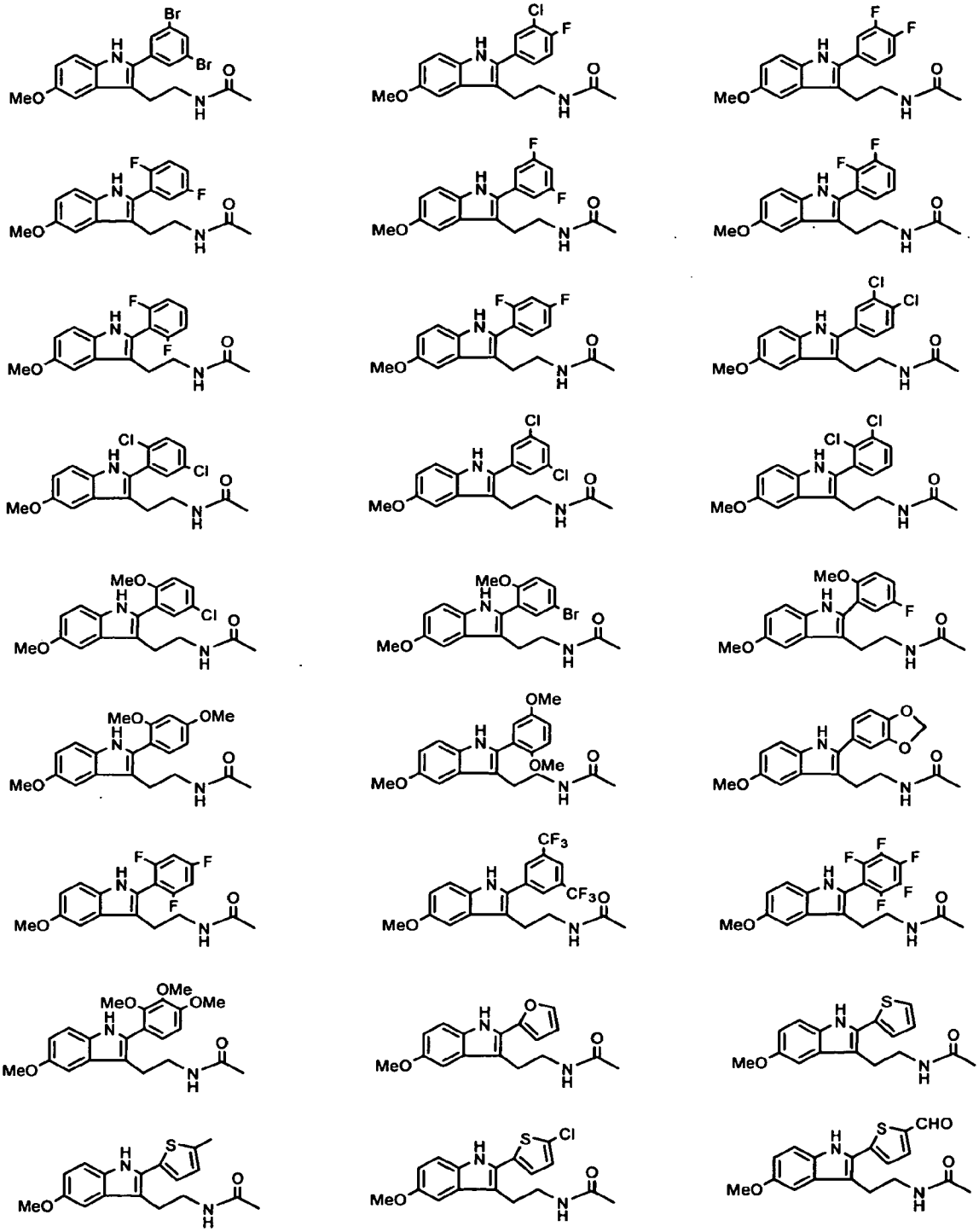
**[0012]** "$C_4$-$C_{20}$ aryl" refers to an aromatic or heteroaromatic ring, including by way of example, phenyl, naphthyl furanyl, thionyl. The aryl ring can be substituted or unsubstituted. Substituents include halo, $C_1$-$C_6$ alkyl, which by way of example can be substituted, for example, by halogen, $C_1$-$C_6$ alkoxy, amino, alkylamino, thiol, alkylthiol, hydroxyl, -CHO, -$NO_2$, phenyl, vinyl, –CN, $Si(CH_3)_3$, -$OCH_2O$-, and combinations thereof. The aryl ring can be substituted with any of one, two, three, four or five, or more substituents, depending on the size of the ring. Examples of $C_4$-$C_{20}$ aryl groups include phenyl, 4-(fluorophenyl), 3-(fluorophenyl), 2-(fluorophenyl), 4-(chlorophenyl), 3-(chlorophenyl), 2-(chlorophenyl), 4-(methylphenyl), 3-(methylphenyl), 2-(methylphenyl), 4-(methoxyphenyl), 3-(methoxyphenyl), 2-(methoxyphenyl), 4-(ethoxyphenyl), 3-(ethoxyphenyl), 2-(ethoxyphenyl), 4-(vinylphenyl), 4-(acetylphenyl), 3-(acetylphenyl), 2-(acetylphenyl), 4-(trifluoromethylphenyl), 3-(trifluoromethylphenyl), 4-(trimethylsilylphenyl), 3-(trimethylsilylphenyl), 4-(methylthiophenyl), 4-(tert-butylphenyl), 4-(dimethylaminophenyl), 4-(ethylphenyl), 4-(benzoxyphenyl), 4-(biphenyl), 2-furanyl, 2-(thiophenyl), 2-(5-methylthiophenyl), 3-(thiophenyl), 2-(indolyl), 1-(naphthalenyl), 2-(naphthalenyl), 4-(dibenzofuranyl), 1-(thianthrenyl), 2,3-(dichlorophenyl), 2,5-(dichlorophenyl), 3,4-(dichlorophenyl), 3,5-(dichlorophenyl), 2,3-(difluorophenyl), 2,4-(difluorophenyl), 2,5-(difluorophenyl), 2,6-(difluorophenyl), 3,4-(difluorophenyl), 3,5-(difluorophenyl), 3,5-(dibromophenyl), 3,5-(bis(trifluoromethyl)phenyl), 2,3-(dimethylphenyl), 2,5-(dimethylphenyl), 2,6-(dimethylphenyl), 3,5-(dimethylphenyl), 2,4-(dimethoxyphenyl), 2,5-(dimethoxyphenyl), 3,4-(dimethoxyphenyl), 2,3,4-(trimethoxyphenyl), 2,4,6-(trifluorophenyl), 2,3,4,5,6-(pentaflurophenyl), and the like.

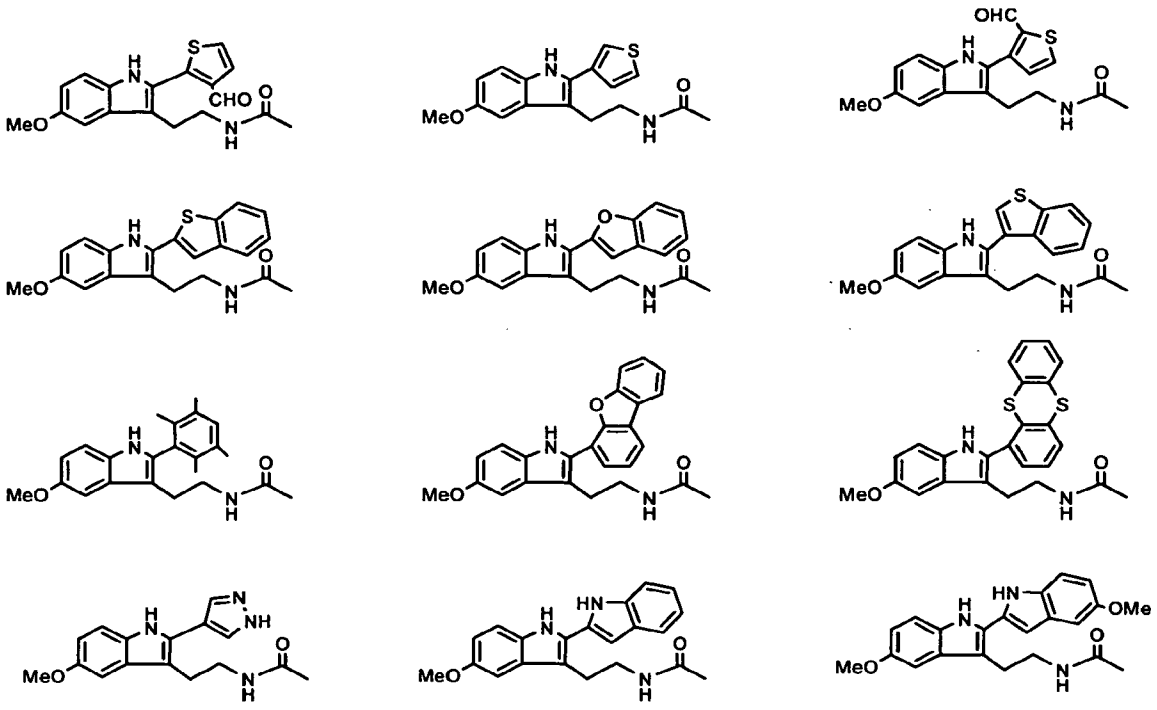
**[0013]** While all of the compounds of Formula II are believed to be useful as a general anesthetic, certain of such compounds are preferred for such use. Preferred compounds of Formula II for use in the invention include those compounds wherein $R_1$ is hydrogen, $R_2$ is a substituted phenyl (preferably 4-substituted phenyl), and $R_3$ is $C_1$ -$C_4$ alkyl (preferably methyl or ethyl).

**[0014]** The following structures are preferred embodiments of the invention:



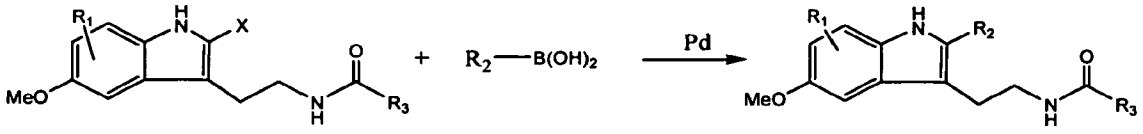

MeO
H
N
O
N
H
OCF3
NO2
CN
SMe
NH2
OH
SiMe3
SH
COOH
NHAc
OMe





**[0015]** Compounds of formula II are preferably prepared by reacting a 2-halo melatonin with aryl boronic acid in the presence of a metal catalyst (e.g., a palladium catalyst) as set forth, for example, in Scheme 1.

**Scheme 1**




x = I or Br

**[0016]** Generally, any 2-halo melatonin analog and any aryl boronic acid can be used for the preparation of the compounds of the invention. Aryl boronic acid is commercially available or it can be prepared according to procedures known in the art. For example, the aryl boronic acid can be prepared from an aryl halide such as is described in, for example, Snieckus, *Chem. Rev.*, *90*, 879 (1990). The 2-bromomelatonin or 2-iodomelatonin starting

material can be prepared according to procedures known in the art (see, e.g., U.S. Patent 5,552,428 and Duranti et al., *Life Sci.*, *51*, 479 (1992)). In a particularly preferred embodiment of the invention, 2-halomelatonin and aryl boronic acid, preferably in the equivalent mole ratio, are heated in the presence of palladium catalyst under argon or nitrogen to about 50-120°C. for 5-10 hours with a mechanical stirrer. The palladium catalyst is removed by filtration and the filtrate is concentrated and purified by column chromatography with ethyl acetate-hexanes (10-50%) as an eluant. The pure product obtained typically is a white or yellow powder. The reaction yields range from 20% to 90%.

**[0017]** Other starting materials that can be employed in the preparation of the 2-aryl melatonin derivatives of the present invention are known and can be made by methods known in the art (see, e.g., U.S. Patents 4,087,444, 4,614,807, and 4,997,845). Methods for the preparation of various indole derivatives are disclosed in, for example, *Heterocycles*, *22(1)*, 195 (1984).

**[0018]** The binding profile of exemplary inventive compounds to neurotransmitter receptor sites is set forth below in Table 1. The characterization of the receptors, isolation of the membrane, and enzyme assay have been described in detail previously (see, e.g., Cole et al., *Life Sci.*, *35*, 1755 (1984), Lawrence et al., *J. Neurochem.*, *45(3)*, 798 (1985), Sweetnam et al., *Mol. Pharmacology*, *29*, 299 (1986), Zarkovsky et al., *Neuropharmacology*, *26 (7A)*, 737 (1987), Li et al., *Eur. J. Pharmacology*, *413*, 63 (2001), and Markela et al., *Mol. Pharmacology, 52*, 380 (1997)).

Table 1

| Chemical | Conc. (M) | Neurotransmitter Related, $GABA_A$ | | | | Ion Channels $Cl^-$, TBOB site |
|---|---|---|---|---|---|---|
| | | Agonist site | BDZ/alpha 1 | BDZ/alpha 5 | BDZ/alpha 6 | |
| Melatonin | 1.0E-3 | -3.11% | 39.80% | 15.19% | 17.50% | 39.44% |
| 6-Chloromelatonin | 1.0E-3 | -13.74% | 12.49% | 13.95% | -7.74% | 43.63% |
| 2-Bromomelatonin | 1.0E-3 | -8.55% | 8.35% | -2.02% | -12.69% | 51.87% |
| 2-phenylmelatonin | 1.0E-4 | 0.33% | 35.16% | 17.92% | 12.48% | 84.28% |
| Luzindole | 1.0E-4 | 5.84% | 5.09% | -1.37% | 4.93% | 47.55% |
| 2-(4-Fluorophenyl) melatonin | 1.0E-4 | nd | 28.80% | 20.59% | 20.76% | 110.10% |
| 2-(4-Trifluoromethylphenyl) melatonin | 1.0E-4 | nd | 8.11% | 17.87% | 25.87% | 103.23% |
| 2-(4-Methylphenyl) melatonin | 1.0E-4 | nd | 10.28% | 22.26% | 32.93% | 101.46% |
| 2-(3-Trifluoromethylphenyl)melatonin | 1.0E-4 | nd | 15.61% | 29.31% | 25.39% | 79.60% |
| 2-(4-Methoxyphenyl) melatonin | 1.0E-4 | nd | -8.16% | 7.09% | 6.68% | 108.82% |
| 2-(4-t-Butoxyphenyl) melatonin | 1.0E-4 | nd | -13.46% | 6.04% | 19.60% | 91.94% |
| 2,6-Diisopropylphenol | 1.0E-4 | 12.48% | -14.31% | -15.58% | -0.89% | 117.52% |

nd: not determined

**[0019]** The compounds of the invention can be formulated into compositions comprising pharmaceutically acceptable carriers for administration to a patient (e.g., a human patient). Any number of suitable pharmaceutically acceptable carriers can be used as a vehicle for the administration of the inventive compounds. Preferably, the inventive compounds are formulated for general pharmaceutical use. Most preferably, the inventive compounds are formulated for use as an anesthetic.

**[0020]** The composition can be administered to a patient (e.g., a human patient) according to conventional methods for anesthesia. Such methods include, for example, oral administration, nasal administration, bolus injection, intravenous administration by repeated doses or by continuous infusion, rectal administration, vaginal administration, sublingual administration, cutaneous administration, and by slow release routes. Preferably, the pharmaceutical composition is administered by continuous infusion. In some embodiments, the pharmaceutical composition can be administered by two or more routes, such as by bolus injection followed by continuous intravenous administration.

**[0021]** Typically, the composition is mixed with, diluted by, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it can be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. Thus, the inventive composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments which contain, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

**[0022]** For oral administration, the 2-aryl substituted melatonin derivatives are incorporated into suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include, for example, synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, or gelatin.

**[0023]** Pharmaceutical compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid compositions can contain suitable pharmaceutically acceptable excipients as set forth above. Preferably the inventive composition is administered orally or nasally for local or systemic effect. Compositions formulated in sterile pharmaceutically acceptable solvents can be nebulised by use of inert gases. Nebulised solutions can be breathed directly from the nebulising device, or the nebulising device can be attached to a face mask, tent, or intermittent positive pressure breathing machine. Compositions in solution, suspension, nanoparticle, or powder can be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

**[0024]** Examples of suitable carriers, excipients, and diluents include, but are not limited to, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, saline solution, syrup, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions can be formulated so as to provide rapid, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

**[0025]** Preferred compositions for administration by injection include those comprising a biologically active melatonin derivative and a surface-active agent (or wetting agent or surfactant) or a derivative in the form of an emulsion (e.g., a water-in-oil or oil-in-water emulsion). Suitable surface-active agents include, but are not limited to, nonionic agents, such as polyoxyethylenesorbitans (e.g., Tween™ 20, 40, 60, 80, or 85) and other sorbitans (e.g., Span™ 20, 40, 60, 80, or 85). Other ingredients such as mannitol or other pharmaceutically acceptable vehicles can be added.

**[0026]** The invention also provides compositions and methods useful for *in vivo* delivery, as well as compositions comprising nanoparticles of the inventive composition that are suitable for parenteral administration in aqueous suspension.

**[0027]** It is well known that colloidal nanoparticles or particles less than 200 nanometers (nm) in size have been widely used in various formulations. The preparation of nanoparticles from biocompatible polymers (e.g., albumin) is disclosed in, for example, U.S. Patents 5,916,596, 6,506,405, and 6,537,579. A large number of conventional pharmacologically active agents circulate in the blood stream bound to carrier proteins (through hydrophobic or ionic interactions), such as, for example, human serum albumin. Thus, compositions comprising the inventive compound and one or more proteins (e.g., human serum albumin) are believed to provide for a pharmacologically active agent that is "pre-bound" to a protein (through hydrophobic or ionic interactions) prior to administration.

**[0028]** In accordance with the invention, nanoparticles of the inventive compound are prepared using a solvent evaporation technique from an oil-in-water emulsion prepared under conditions of high shear forces (e.g., sonication, high pressure homogenization, or the like).

**[0029]** The invention also provides submicron particles in powder form, which can easily be reconstituted in water or saline. The powder is obtained after removal of water by lyophilization. Preferably, human serum albumin serves as the structural component of the nanoparticles of the inventive compound, as well as a cryoprotectant and reconstitution aid. The preparation of particles filterable through a 0.22 micron filter according to the method as described herein, followed by drying or lyophilization, produces a sterile solid formulation useful for intravenous injection.

**[0030]** Several biocompatible materials can be employed in the practice of the present invention for the formation of a polymeric shell. Suitable biocompatible materials include, for example, naturally occurring materials such as proteins, polypeptides, oligopeptides, polynucleotides, polysaccharides (e.g., starch, cellulose, dextrans, alginates, chitosan, pectin, hyaluronic acid, and the like), and lipids. Examples of suitable proteins that can be used in the invention include albumin, insulin, hemoglobin, lysozyme, immunoglobulins, α-2-

macroglobulin, fibronectin, vitronectin, fibrinogen, casein, and the like, as well as combinations of any two or more thereof. Alternatively, the biocompatible material can be prepared using synthetic polymers. Examples of suitable synthetic polymers include polyalkylene glycols (e.g., linear or branched chain), polyvinyl alcohol, polyacrylates, polyhydroxyethyl methacrylate, polyacrylic acid, polyethyloxazoline, polyacrylamides, polyisopropyl acrylamides, polyvinyl pyrrolidinone, polylactide/glycolide and the like, and combinations thereof.

**[0031]** The inventive pharmaceutical composition can optionally employ a dispersing agent to suspend or dissolve the inventive compound. Preferred dispersing agents include, for example, volatile liquids such as dichloromethane, chloroform, ethyl acetate, benzene, and the like (e.g., solvents that have a high degree of solubility for the pharmacologically active agent, and are soluble in the other dispersing agent employed), in combination with a less volatile dispersing agent. The addition of volatile additives enhances the solubility of the pharmacologically active agent into the dispersing agent. Following dissolution, the volatile component can be removed by evaporation (e.g., under vacuum).

**[0032]** The inventive pharmaceutical composition can be used for general anesthesia to facilitate surgery, drug or alcohol withdrawal, treatment of tetanus, and other diagnostic or therapeutic interventions. In particular, the present invention can be used to maintain general anesthesia for extended periods (e.g., 24-48 hours) in addicted patients during drug and/or alcohol withdrawal. The invention can be used to maintain general anesthesia for prolonged periods (e.g., days to weeks) in the management of patients with tetanus. The inventive pharmaceutical composition can also be used to render patients sedated and pain-free to facilitate surgical and other therapeutic interventions (e.g., endotracheal mechanical ventilation and wound dressing change in patients with burns), or diagnostic procedures (e.g., endoscopy and imaging techniques) for which loss of consciousness is not required (i.e., "conscious sedation").

**[0033]** The invention further provides a method for treating a condition affected by melatonin activity in a patient. The method comprises administering to the patient a therapeutically effective amount of the inventive pharmaceutical composition. Any condition affected by melatonin activity can be treated by the inventive method. Examples of such conditions include, for example, depression, epilepsy, work-shift syndrome, sleep and chronobiological disorders, glaucoma, reproduction, premenstrual syndrome, immune disorders, inflammatory articular diseases, neuroendocrine disorders, sleep disorders associated with jet lag, neurodegenerative diseases of the central nervous system (e.g.,

Parkinson's disease or Alzheimer's disease), and certain types of cancer. The inventive pharmaceutical composition also can be used as a contraceptive or as an analgesic.

**[0034]** The following examples further illustrate the invention but, of course, should not be construed as in any way limiting in its scope.

EXAMPLE 1

**[0035]** This example illustrates the preparation of N-(2-(2-bromo-5-methoxy-1H-indol-3-yl)ethyl)acetamide. Melatonin (2.0 g, 8.61 mmol) was dissolved in a mixture of THF (40 mL) and $CHCl_3$ (40 mL). Pyridinium tribromide (3.5 g, 10.3 mmol) was added, and the mixture was stirred for 35 minutes at 0 °C. Aqueous NaOH (2 N) was added to quench the reaction and adjust the solution to pH13. The mixture was extracted with ethyl acetate (200 mL), and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. After condensation, the crude product was purified by flash column chromatography (hexanes:ethyl acetate, 1:1) and a colorless solid (1.9 g, 6.13 mmol, 71%) was obtained. $^1H$ NMR ($CDCl_3$, 400 MHz): 8.19 (brs, 1H), 7.20 (dd, $J$ = 8.8, 2.9 Hz, 1H), 6.97 (d, $J$ = 2.4 Hz, 1H), 6.84 (dd, $J$ = 8.9, 2.4 Hz, 1H), 5.66 (brs, 1H), 3.85 (s, 3H), 3.53 (dd, $J$ = 13.5, 6.4 Hz, 2H), 2.92 (t, $J$ = 6.6 Hz, 2H), 1.94 (s, 3H). ESI-MS: calcd. for $C_{13}H_{16}BrN_2O_2$ ($MH^+$) 311, found 311.

EXAMPLE 2

**[0036]** This example illustrates the preparation of N-(2-(2-(4-fluorophenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide. N-(2-(2-bromo-5-methoxy-1H-indol-3-yl)ethyl)acetamide (275 mg, 0.89 mmol) was dissolved in a mixture of toluene (11 mL) and ethanol (11 mL). 4-fluorophenylboronic acid (186 mg, 1.33 mmol), LiCl (113 mg, 2.66 mmol) and aqueous sodium carbonate (2.2 mL, 1M) were sequentially added to the solution. Palladium (5 mg) was then added in the presence of an argon atmosphere. The mixture was refluxed for 4 hours, and the crude product was purified via flash column chromatography (hexanes:ethyl acetate, 1:1). The final product was a yellow solid (221 mg, 76%). $^1H$ NMR ($CDCl_3$, 500 MHz): 8.08 (brs, 1H), 7.52 (dd, $J$ = 8.8, 5.4 Hz, 2H), 7.29-7.16 (m, 4H), 6.88 (dd, $J$ = 8.6, 2.3 Hz, 1H), 3.88 (s, 3H), 3.51 (dd, $J$ = 12.8, 6.9 Hz, 2H), 3.05 (t, $J$ = 7.0 Hz, 2H), 1.82 (s, 3H). ESI-MS: calcd. for $C_{19}H_{19}FN_2O_2Na$ ($M+Na^+$) 349, found 349.

EXAMPLE 3

**[0037]** This example illustrates the preparation of N-(2-(5-methoxy-2-phenyl-1H-indol-3-yl)ethyl)acetamide. N-(2-(2-bromo-5-methoxy-1H-indol-3-yl)ethyl)acetamide (248 mg, 0.8 mmol) was dissolved in a mixture of toluene (9.5 mL) and ethanol (9.5 mL). Phenylboronic acid (145 mg, 1.19 mmol), LiCl (102 mg, 2.41 mmol), and aqueous sodium carbonate (2 mL, 1M) were sequentially added to the solution. Palladium was then added to the mixture in the

presence of an argon atmosphere. The mixture was refluxed for 5 hours, and the crude product was purified via flash column chromatography (hexanes:ethyl acetate, 1:1). The final product was yellow solid (130 mg, 53%). $^1$H NMR ($CDCl_3$, 500 MHz): 8.00 (brs, 1H), 7.56 (dd, $J$ = 7.9 Hz, 2H), 7.48 (t, $J$ = 7.5 Hz, 2H), 7.38 (t, $J$ = 7.4 Hz, 1H), 7.29 (d, $J$ = 8.7 HZ, 1H), 7.10 (d, $J$ = 2.3 Hz, 1H), 6.89 (dd, $J$ = 8.8, 2.4 Hz, 1H), 5.46 (brs, 1H), 3.89 (s, 3H), 3.55 (dd, $J$ = 12.5, 6.4 Hz, 2H), 3.11 (t, $J$ = 6.7 Hz, 2H), 1.78 (s, 3H). ESI-MS: calcd. for $C_{19}H_{21}N_2O_2$ ($MH^+$) 309, found 309.

EXAMPLE 4

**[0038]** This example illustrates the preparation of N-(2-(5-methoxy-2-methoxyphenyl-1H-indol-3-yl)ethyl)acetamide. N-(2-(2-bromo-5-methoxy-1H-indol-3-yl)ethyl)acetamide (286 mg, 0.92 mmol) was dissolved in a mixture of toluene (11 mL) and ethanol (11 mL.). 4-methoxyphenylboronic acid (210 mg, 1.38 mmol), LiCl (117 mg, 2.76 mmol), and aqueous sodium carbonate (2.3 mL, 1M) were sequentially added to the solution. Palladium was then added to the mixture in the presence of an argon atmosphere. The mixture was refluxed for 3 hours, and the crude product was purified by flash column chromatography (hexanes:ethyl acetate, 2:3). The final product was a yellow solid (280 mg, 90%). $^1$H NMR ($CDCl_3$, 500 MHz): 8.01 (brs, 1H), 7.50-7.42 (m, 3H), 7.07-6.87 (m, 3H), 6.86 (dd, $J$ = 8.7, 2.4 Hz, 1H), 5.49 (brs, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.53 (dd, $J$ = 13.0, 6.8 Hz, 2H), 3.06 (t, $J$ = 6.9 Hz, 2H), 1.80 (s, 3H). ESI-MS: calcd. for $C_{20}H_{22}N_2O_3Na$ ($M+Na^+$) 361, found 361.

EXAMPLE 5

**[0039]** This example illustrates the preparation of N-(2-(5-methoxy-2-p-tolyl-1H-indol-3-yl)ethyl)acetamide. N-(2-(2-bromo-5-methoxy-1H-indol-3-yl)ethyl)acetamide (258 mg, 0.83 mmol) was dissolved in a mixture of toluene (10 mL) and ethanol (10 mL). 4-methylphenylboronic acid (169 mg, 1.24 mmol), LiCl (106 mg, 2.49 mmol) and aqueous sodium carbonate (2.1 mL, 1M) were sequentially added to the solution. Palladium (5 mg) was then added in the presence of an argon atmosphere. The mixture was refluxed for 4.5 hours, and the crude product was purified on flash column chromatography (hexanes:ethyl acetate, 1:2). The final product was a yellow foam (221 mg, 83%). $^1$H NMR ($CDCl_3$, 500 MHz): 7.99 (s, 1H), 7.47-7.44 (m, 2H), 7.29-7.26 (m, 3H), 7.08 (d, $J$ = 2.4 Hz, 1H), 6.87 (dd, $J$ = 8.8, 2.4 Hz, 1H), 5.45 (brs, 1H), 3.88 (s, 3H), 3.54 (dd, $J$ = 12.7, 6.8 Hz, 2H), 3.09 (t, $J$ = 6.8 Hz, 2H), 2.41 (s, 3H), 1.78 (s, 3H). ESI-MS: calcd. for $C_{20}H_{22}N_2O_2Na$ ($M+Na^+$) 345, found 345.

EXAMPLE 6

**[0040]** This example illustrates the preparation of N-(2-(2-(4-tert-butylphenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide. N-(2-(2-bromo-5-methoxy-1H-indol-3-

yl)ethyl)acetamide (280 mg, 0.90 mmol) was dissolved in a mixture of toluene (11 mL) and ethanol (11 mL). 4-*t*-butylphenylboronic acid (186 mg, 1.35 mmol), LiCl (114 mg, 2.69 mmol) and aqueous sodium carbonate (2.3 mL, 1M) were sequentially added to the solution. Palladium (5 mg) was then added in the presence of an argon atmosphere. The mixture was refluxed for 3.5 hours, and the crude product was purified by flash column chromatography (hexanes:ethyl acetate, 3:2). The final product was a lavender solid (171 mg,52%). $^1$H NMR ($CDCl_3$, 500 MHz): 8.04 (brs, 1H), 7.50 (s, 4H), 7.28 (d, $J$ = 8.8 Hz, 1H), 7.08 (d, $J$ = 2.4 Hz,1H), 6.87 (dd, $J$ = 8.7, 2.4 Hz, 1H), 5.48 (brs, 1H), 3.88 (s, 3H), 3.55 (dd, $J$ = 12.7, 6.6 Hz, 2H), 3.10 (t, $J$ = 6.6 Hz, 2H), 1.76 (s, 3H), 1.36 (s, 9H). ESI-MS: calcd. for $C_{23}H_{28}N_2O_2Na$ ($M+Na^+$) 387, found 387.

EXAMPLE 7

**[0041]** This example illustrates the preparation of N-(2-(2-(3-trifluoromethylphenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide. N-(2-(2-bromo-5-methoxy-1H-indol-3-yl)ethyl)acetamide (295 mg, 0.95 mmol) was dissolved in a mixture of toluene (11 mL) and ethanol (11 mL). 3-trifluoromethylphenylboronic acid (271 mg, 1.42 mmol), LiCl (121 mg, 2.85 mmol), and aqueous sodium carbonate (2.4 mL, 1M) were added sequentially. Palladium (5 mg) was then added in the presence of an argon atmosphere. The mixture was refluxed for 5 hours, and the crude product purified by flash column chromatography (hexanes:ethyl acetate, 3:2). The final product was a lavender solid (200 mg, 56%). $^1$H NMR ($CDCl_3$, 500 MHz): 8.15 (brs, 1H), 7.77 (d, $J$ = 1.4 Hz, 2H), 7.61-7.59 (m, 3H), 7.30 (d, $J$ = 8.8 Hz, 1H), 7.11 (d, $J$ = 2.4 Hz, 1H), 6.92 (dd, $J$ = 9.0, 2.4 Hz, 1H), 5.55 (brs, 1H), 3.89 (s, 3H), 3.55 (dd, $J$ = 13.2, 6.8 Hz, 2H), 3.09 (t, $J$ = 7.0 Hz, 2H), 1.82 (s, 3H). ESI-MS: calcd. for $C_{20}H_{19}F_3N_2O_2Na$ ($M+Na^+$) 399, found 399.

EXAMPLE 8

**[0042]** This example illustrates the preparation of N-(2-(2-(4-trifluoromethylphenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide. N-(2-(2-bromo-5-methoxy-1H-indol-3-yl)ethyl)acetamide (282 mg, 0.91 mmol) was dissolved in a mixture of toluene (12 mL) and ethanol (12 mL). 4-trifluoromethylphenylboronic acid (173 mg, 0.91 mmol), LiCl (116 mg, 2.73 mmol), and aqueous sodium carbonate (2.2 mL, 1M) were added sequentially. Palladium (5 mg) was then added in the presence of an argon atmosphere. The mixture was refluxed for 4 hours, and the crude product was purified by flash column chromatography (hexanes:ethyl acetate, 1:1). The final product was a lavender solid (168 mg, 49%). $^1$H NMR ($CDCl_3$, 500 MHz): 7.44-7.69 (m, 6H), 7.31 (d, $J$ = 8.7 Hz, 1H), 7.11 (d, $J$ = 2.3 Hz, 1H), 6.92 (dd, $J$ = 8.8, 2.4 Hz, 1H), 3.89 (s, 3H), 3.55 (dd, $J$ = 11.8, 6.6 Hz, 2H), 3.11 (t, $J$ = 7.1 Hz, 2H), 1.84 (s, 3H). ESI-MS: calcd. for $C_{20}H_{19}F_3N_2O_2Na$ ($M+Na^+$) 399, found 399.

EXAMPLE 9

**[0043]** This example illustrates the preparation of a pharmaceutical composition comprising an inventive melatonin derivative and albumin. 30 mg N-(2-(2-(4-fluorophenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide (as prepared in Example 2) was dissolved in 3.0 mL methylene chloride/methanol (9/1). The solution was added to 27.0 mL of a human serum albumin solution (3% w/v). The mixture was homogenized for 5 minutes at low RPM (Vitris homogenizer, model Tempest I.Q.) to form a crude emulsion, and transferred into a high pressure homogenizer (Avestin). Emulsification was performed at 9000-40,000 psi for at least 5 cycles. The resulting system was transferred into a Rotavap and solvent was rapidly removed at 40 °C, at reduced pressure (30 mm Hg), for 20-30 minutes. The resulting dispersion was translucent and the typical average diameter of the resulting particles was in the range 50-220 nm (Z-average, Malvern Zetasizer). The dispersion was further lyophilized for 48 hours. The resulting cake was easily reconstituted to the original dispersion by addition of sterile water or saline. The particle size after reconstitution was the same as before lyophilization. It should be recognized that the amounts, types and proportions of drug, solvents, proteins used in this example are not limiting in anyway.

EXAMPLE 10

**[0044]** This example illustrates the formation of nanoparticles of the inventive compound by using cavitation and high shear forces during a sonication process. Thus, 20 mg N-(2-(2-(4-fluorophenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide (as prepared in Example 2) was dissolved in 1.0 ml methylene chloride. The solution was added to 4.0 ml of a human serum albumin solution (5% w/v). The mixture was homogenized for 5 minutes at low RPM (Vitris homogenizer, model Tempest I.Q.) to form a crude emulsion, and transferred into a 40 kHz sonicator cell. Sonication was performed at 60-90% power at 0 °C for 1 minute (550 Sonic Dismembrator). The mixture was transferred into a Rotary evaporator, and methylene chloride was rapidly removed at 40 °C, at reduced pressure (30 mm Hg), for 20-30 minutes. The diameter of the resulting particles was 300-420 nm (Z-average, Malvern Zetasizer).

**[0045]** The dispersion was further lyophilized for 48 hrs without adding a cryoprotectant. The resulting cake was easily reconstituted to the original dispersion by addition of sterile water or saline. The particle size after reconstitution was the same as before lyophilization.

EXAMPLE 11

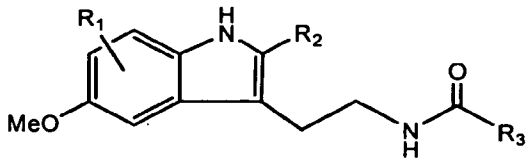
**[0046]** This example illustrates the effectiveness of the inventive compound in inducing general anesthesia in rats. All experiments are carried out in male Sprague-Dawley rats (300–350 g) (Harlan, Indianapolis, IN). Rats are maintained on a 12 hour light/12 hour dark cycle with free access to food and water. All surgical procedures are performed under aseptic

conditions. Non-fasting rats are anesthetized with isoflurane and weighed. In all rats and in all studies, the right jugular vein is cannulated with a heparinized (20 U/ml) saline-filled (PE60 50) catheter. The free end of the tubing is tunneled subcutaneously to exit posterior to the occiput, trimmed to remove excess length, and capped.

**[0047]** N-(2-(2-(4-fluorophenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide (as prepared in Example 2) is prepared for anesthetic use in the routine solvent. To initially determine the anesthetic effects of the compound, are be injected intravenously with various doses of the compound. Each rat receives three doses of drug in a cumulative manner at 1-2 minute intervals. The loss of righting reflex is used as an index of hypnosis (see, e.g., Miller et al., *Anesthesiology, 36,* 339-51 (1972)). Abolition of the withdrawal response to noxious stimulation (nocifensive response) is used to define the state of surgical anesthesia. For righting reflex, the animal is placed on its back and attempts to reassume the prone position within 15 seconds is noted. Nocifensive stimuli are tested by application of a 1-cm serrated alligator clip to the middle third of the tail. The clip is oscillated for 1 minute or until the rat responds by purposeful movement of extremities or head. Movement response of the extremities, or head to tail clamping is well established. In addition to recording the occurrence of nocifensive movement, the latency to movement is measured to the nearest second. Rats in which application of the clip does not elicit nocifensive movement are assigned the cutoff latency of 60 seconds.

WHAT IS CLAIMED IS:

1. A compound of the formula




wherein

$R_1$ is hydrogen, halo, or nitrate,

$R_2$ is $C_4$-$C_{20}$ aryl, and

$R_3$ is $C_1$–$C_6$ alkyl or $C_1$–$C_6$ alkoxy.

2. The compound of claim 1, wherein $R_1$ is hydrogen, $R_2$ is $C_4$-$C_{20}$ aryl, and $R_3$ is methyl.

3. The compound of claim 1, wherein $R_1$ is hydrogen, $R_2$ is $C_4$-$C_{20}$ aryl, and $R_3$ is ethyl.

4. The compound of claim 1, wherein $R_1$ is hydrogen, $R_2$ is $C_4$-$C_{20}$ aryl, and $R_3$ is cyclopropyl.

5. The compound of claim 1, wherein $R_1$ is hydrogen, $R_2$ is $C_4$-$C_{20}$ aryl, and $R_3$ is cyclobutyl.

6. The compound of claim 1, wherein $R_1$ is hydrogen, $R_2$ is $C_4$-$C_{20}$ aryl, and $R_3$ is methoxy.

7. The compound of claim 1, wherein $R_1$ is hydrogen, $R_2$ is $C_4$-$C_{20}$ aryl, and $R_3$ is ethoxy.

8. The compound of any of claims 2-7, wherein $R_2$ is selected from the group consisting of phenyl, 4-(fluorophenyl), 3-(fluorophenyl), 2-(fluorophenyl), 4-(chlorophenyl), 3-(chlorophenyl), 2-(chlorophenyl), 4-(methylphenyl), 3-(methylphenyl), 2-(methylphenyl), 4-(methoxyphenyl), 3-(methoxyphenyl), 2-(methoxyphenyl), 4-(ethoxyphenyl), 3-

(ethoxyphenyl), 2-(ethoxyphenyl), 4-(vinylphenyl), 4-(acetylphenyl), 3-(acetylphenyl), 2-(acetylphenyl), 4-(trifluoromethylphenyl), 3-(trifluoromethylphenyl), 4-(trimethylsilylphenyl), 3-(trimethylsilylphenyl), 4-(methylthiophenyl), 4-(tert-butylphenyl), 4-(dimethylaminophenyl), 4-(ethylphenyl), 4-(benzoxyphenyl), 4-(biphenyl), 2-furanyl, 2-(thiophenyl), 2-(5-methylthiophenyl), 3-(thiophenyl), 2-(indolyl), 1-(naphthalenyl), 2-(naphthalenyl), 4-(dibenzofuranyl), 1-(thianthrenyl), 2,3-(dichlorophenyl), 2,5-(dichlorophenyl), 3,4-(dichlorophenyl), 3,5-(dichlorophenyl), 2,3-(difluorophenyl), 2,4-(difluorophenyl), 2,5-(difluorophenyl), 2,6-(difluorophenyl), 3,4-(difluorophenyl), 3,5-(difluorophenyl), 3,5-(dibromophenyl), 3,5-(bis(trifluoromethyl)phenyl), 2,3-(dimethylphenyl), 2,5-(dimethylphenyl), 2,6-(dimethylphenyl), 3,5-(dimethylphenyl), 2,4-(dimethoxyphenyl), 2,5-(dimethoxyphenyl), 3,4-(dimethoxyphenyl), 2,3,4-(trimethoxyphenyl), 2,4,6-(trifluorophenyl), and 2,3,4,5,6-(pentaflurophenyl).

9. The compound of claim 1, wherein the compound is N-(2-(2-(4-fluorophenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide.

10. The compound of claim 1, wherein the compound is N-(2-(5-methoxy-2-methoxyphenyl-1H-indol-3-yl)ethyl)acetamide.

11. The compound of claim 1, wherein the compound is N-(2-(5-methoxy-2-p-tolyl-1H-indol-3-yl)ethyl)acetamide.

12. The compound of claim 1, wherein the compound is N-(2-(2-(4-tert-butylphenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide.

13. The compound of claim 1, wherein the compound is N-(2-(2-(3-trifluoromethylphenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide.

14. The compound of claim 1, wherein the compound is N-(2-(2-(4-trifluoromethylphenyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide.

15. A method for preparing the compound of claim 1, which method comprises reacting a 2-halo melatonin with aryl boronic acid in the presence of palladium catalyst.

16. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

17. The pharmaceutical composition of claim 16, wherein the pharmaceutical composition comprises nanoparticles of the compound of claim 1.

18. The pharmaceutical composition of claim 16, wherein the pharmaceutical composition comprises an anesthetic inducing effective amount of the compound of claim 1 and a pharmaceutically acceptable anesthetic carrier.

19. A method of inducing sedation, hypnosis and/or sleep, or general anesthesia in a patient, which method comprises administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 16.

20. The method of claim 19, wherein said administering is by a method selected from the group consisting of oral administration, nasal respiratory administration, bolus injection, intravenous administration, continuing infusion, rectal administration, vaginal administration, sublingual administration, and cutaneous administration.

21. A method for treating sleep disorders or chronobiological disorders in a patient, which method comprises administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 16.

22. A method for treating a condition affected by melatonin activity in a patient, which method comprises administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 16.

23. The method of claim 22, wherein the condition affected by melatonin activity is selected from the group consisting of depression, epilepsy, jet-lag, work-shift syndrome, sleep disorders, glaucoma, reproduction, cancer, premenstrual syndrome, immune disorders, inflammatory articular diseases, neurodegenerative diseases of the central nervous system, and neuroendocrine disorders.

ABSTRACT

The invention provides 2-aryl substituted derivatives of melatonin. The invention further provides pharmaceutical compositions comprising such derivatives, methods for preparing such derivatives, and methods of using such derivatives to induce general anesthesia, sedation, and/or hypnotic or sleep effects in a patient, and to treat conditions affected by melatonin activity in a patient.

**Application Data She t**

**APPLICATION INFORMATION**

| | |
|---|---|
| Application Number:: | |
| Filing Date:: | December 23, 2003 |
| Application Type:: | Provisional |
| Subject Matter:: | Utility |
| Suggested classification:: | |
| Suggested Group Art Unit:: | |
| CD-ROM or CD-R?:: | None |
| Number of CD Disks: | |
| Number of Copies of CDs:: | |
| Sequence Submission?:: | |
| Computer Readable Form (CRF)?:: | No |
| Number of Copies of CRF:: | |
| Title:: | SUBSTITUTED MELATONIN DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND METHODS OF USE |
| Attorney Docket Number:: | 225630 |
| Request for Early Publication?:: | No |
| Request for Non-Publication?:: | No |
| Suggested Drawing Figure:: | |
| Total Drawing Sheets:: | |
| Small Entity?:: | Yes |
| Latin Name:: | |
| Variety denomination name:: | |
| Petition Included?:: | No |
| Petition Type:: | |
| Licensed US Govt. Agency:: | |
| Contract or Grant Numbers:: | |
| Secrecy Order in Parent Appl.?:: | No |

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Representative Customer Number:: 23460

| Representative Designation:: | Registration Number:: | Representative Name:: |
|---|---|---|

## DOMESTIC PRIORITY INFORMATION

| Application:: | Continuity Type:: | Parent Application:: | Parent Filing Date:: |
|---|---|---|---|

## FOREIGN APPLICATION INFORMATION

| Country:: | Application Number:: | Filing Date:: | Priority Claimed |
|---|---|---|---|

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| State or Province of Mailing address:: | California |
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